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Lower Body Mass Index at Baseline Is Related to Steeper Cognitive Decline in the Alzheimer's Disease Neuroimaging Initiative Cohort

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ABSTRACT

Objective: Midlife obesity is a risk factor for dementia, whereas obesity in older age may be protective of cognition, a phenomenon known as the "obesity paradox." The mechanisms underlying this phenomenon and the relationship between body mass index (BMI) and cognitive function over time remain unclear.

Methods: In 1399 adults with and without mild cognitive impairment (median age 73.6 years) from the Alzheimer's Disease Neuroimaging Initiative, we modeled the effects of baseline BMI on within-person trajectories of cognitive decline using Latent Growth Curve Modeling. We also tested if the effects of BMI on cognitive decline are global or specific to memory, executive function, or language.

Results: Higher baseline BMI was associated with better memory ($\beta_{BMI} = 0.06$, $p < .05$) and worse executive function ($\beta_{BMI} = -0.05$, $p < .05$) and not associated with language. Independent of baseline diagnosis, higher baseline BMI was associated with slower rate of decline in executive function, memory, and language ($\beta_{BMI} = 0.13$, 0.12, and 0.12, respectively; $p < .01$). Higher BMI was not associated with the intercept ($\beta_{BMI} = 0.04$, $p = .059$) or change ($\beta_{BMI} = 0.04$, $p = .415$) in a global cognitive factor.

Conclusions: We found that higher baseline BMI was associated with slower cognitive decline in participants with and without mild cognitive impairment diagnosis. Higher BMI in this context seems to be protective of cognitive function for people at risk for dementia. Our findings also support domain-specific effects of obesity on various cognitive functions rather than a final common pathway.

Key words: obesity, body mass index, cognitive function, mild cognitive impairment, structural equation modeling.

INTRODUCTION

Excessive adipose tissue accumulation in midlife has been recognized as a significant risk factor for developing dementia in later life (1–4). Individuals meeting the clinical criteria for obesity as middle-aged adults are three times more likely to receive a diagnosis of Alzheimer's disease (AD) in older age and five times more likely to experience vascular dementia than those whose midlife weight was in the recommended range (5). At the same time, it has become increasingly clear that the relationship between body adiposity and cognitive function throughout the life span is complex. The term *obesity paradox*, initially applied to cardiovascular disease, was used to describe better clinical outcomes for patients with established cardiovascular disease and obesity, which was largely unexpected given that obesity has been considered a major contributor to the pathogenesis of cardiovascular disease and is significantly associated with increased overall mortality (6). Similar paradoxical findings have emerged within the cognitive aging literature, as some studies highlight obesity in midlife has been associated with an increased risk of developing dementia later in life, whereas others suggest that obesity in older age (>65 years) is considered protective of cognition (7). The precise mechanisms of neurodegeneration or neuroprotection linked to body adiposity are yet to be fully elucidated. The issue is also far from settled as to whether the effect of peripheral adiposity on the brain is global, impacting all domains of cognitive function equally, through some shared mechanism, or specific, impacting specific cognitive domains differentially. For example, some studies have linked excess adipose tissue to cortical thinning in the medial temporal lobe and hippocampus (8) and diminished neuronal viability in memory-related regions (9), supporting reports associating obesity with impaired memory function (10). Other studies point toward obesity having an impact on attention-executive

AD = Alzheimer's disease, **ADNI** = Alzheimer's Disease Neuroimaging Initiative, **BMI** = body mass index, **CFI** = comparative fit index, **CU** = cognitively unimpaired, **Dx** = diagnosis, **LGM** = Latent Growth Curve Modeling, **MCI** = mild cognitive impairment, **RMSEA** = root mean square error of approximation

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function (11) through deleterious effects on peripheral and cerebral vasculature, potentially resulting in damage to white matter integrity due to hypoperfusion (12,13). However, others have argued that obesity-related systemic and central inflammation may converge into a final common pathway leading to cognitive impairment via disruption of hypothalamic circuits (14).

Testing the assumption that optimal weight range may not be the same for all individuals across the life span or whether the effects of obesity on cognitive function are global or specific is challenging. Currently, there are few longitudinal studies that examine both body composition and cognitive function in depth and with sufficient follow-up to allow for more sophisticated approaches such as multivariate growth curve analysis of decline across multiple domains of cognitive functioning (15). The data set collected as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) provides a unique opportunity to track progression of cognitive impairment in older adults over multiple waves of data, using important biomarkers including body mass index (BMI). The data set also includes a rich test battery covering multiple cognitive domains facilitating hypotheses related to the extent to which cognitive changes related to obesity in older age might be coupled. Because the median age of ADNI participants at baseline is greater than 70 years, we hypothesized that, if the obesity paradox was evident in this data set, greater baseline BMI would relate to better cognitive performance at baseline and less decline over time in individuals not meeting the AD criteria at baseline, adjusting for preexisting mild cognitive impairment (MCI). Individuals already meeting the clinical criteria for AD at baseline were excluded from this analyses because the onset of dementia is well known to be related to frailty (16). In terms of global versus specific effects of BMI on cognitive decline, we hypothesized that BMI at baseline will be associated with global cognitive change, following the theory that obesity-related neuroinflammation may be the final common pathway for cognitive impairment in obesity (14). This hypothesis is also supported by evidence from the cognitive aging literature suggesting that a substantial proportion of the variance in cognitive change over time is shared by different cognitive domains (15).

METHODS

Data Set

This project used data from the publicly available ADNI (http://adni.loni.usc.edu), a public-private partnership established in 2003 that sought to enhance our understanding of the progression of MCI to AD in older adults. The study uses a combination of magnetic resonance imaging, positron emission tomography, cerebrospinal fluid and blood biomarkers, and clinical and neuropsychological assessments, most of which are completed annually. For more information, see http://www.adni-info.org. The ADNI protocols were approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all study participants before enrollment, in accordance with the ethical principles of the Helsinki Declaration for engagement in medical research.

Participants and Inclusion/Exclusion Criteria

Enrollment criteria are described in detail in the original study protocol publication (17). Adults were eligible for participation if they were between the ages of 55 and 90 years, had more than 6 years of education or work-history equivalent, were fluent in English or Spanish, had vision and hearing corrected to normal, and did not show signs of significant neurologic disease (e.g., schizophrenia, stroke) or history of traumatic brain injury. As part of the study, participants were evaluated for meeting the criteria for AD or MCI at study entry using the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria, and enrolled cognitively unimpaired (CU) control participants were matched on age and determined to be without memory complaints or significant impairment in cognitive functioning or independent activities of daily living (17). Participants with current cognitive complaints and those at high risk for cognitive decline were explicitly recruited; therefore, the data set is enriched with patients meeting the criteria for MCI and AD at baseline (~50% of the participants in the sample).

A total of 1735 ADNI participants had all available key demographic information (e.g., age, education, sex) and neuropsychological MCI/AD diagnostic groupings assessed at baseline. Participants with baseline diagnosis of AD were excluded from this analysis because of documented links between AD and frailty (16) ($N = 331$). Five participants were missing baseline BMI data resulting in a final sample of 1399. Follow-up cognitive data were available for 1211 adults at 12 months (13% attrition), 1115 adults at 24 months (20% attrition), 789 adults at 36 months (44% attrition), and 611 adults at 48 months (56% attrition) after baseline. Participants were classified as CU or MCI at baseline (see diagnostic criteria information hereinafter). Sample characteristics can be seen in Table 1.

Assessment of Cognitive Functioning

Participants completed a battery of neuropsychological tests including measures of attention/executive functioning (Trail Making Test Parts A and B), verbal memory (Immediate and Delayed Recall and Recognition Total from Story A of the Weschler Memory Scale—Revised; Delayed Recall and Recognition Total of the Rey Auditory Verbal Learning Test), and language (Boston Naming Test or Multilingual Naming Test; animal fluency). Raw scores for each of the measures representing the cognitive subdomains were converted to *z* scores based on predicted values from regression equations (adjusted for age, sex, and education) derived from a robust control group of individuals who have demonstrated intact cognitive function for the entire duration of participation in ADNI (18,19). Memory, attention/executive, and language domain composite scores were created by averaging the *z* scores across tests within each cognitive subdomain. Participants included in this study were evaluated for meeting the criteria for cognitive impairment using Jak/Bondi actuarial neuropsychological criteria for MCI, given that these criteria have been shown to improve biomarker and cognitive associations over time relative to traditional ADNI MCI diagnostic criteria (18,19). Of the 1399 participants, 811 were classified as unimpaired (CU) at baseline, whereas 588 were classified as impaired (MCI).

Body Mass Index

Height and weight were measured at baseline on a physician's beam balance scale for the subsequent calculations of BMI. BMI was calculated by dividing weight in kilograms by height in meters squared.

TABLE 1. Sample Characteristics

	Cognitively Unimpaired (n = 811)	MCI (n = 588)	Overall (N = 1399)
Age, y			
Mean (SD)	73.5 (6.92)	73.5 (7.20)	73.5 (7.04)
Median [min, max]	73.4 [55.0, 91.4]	74.2 [54.4, 88.4]	73.6 [54.4, 91.4]
Education			
Mean (SD)	16.3 (2.71)	15.8 (2.91)	16.1 (2.81)
Median [min, max]	16.0 [6.00, 20.0]	16.0 [4.00, 20.0]	16.0 [4.00, 20.0]
Sex			
Mean (SD)	0.464 (0.499)	0.425 (0.495)	0.447 (0.497)
Median [min, max]	0 [0, 1.00]	0 [0, 1.00]	0 [0, 1.00]
Race			
Am Indian/Alaskan	2 (0.2%)	1 (0.2%)	3 (0.2%)
Asian	11 (1.4%)	11 (1.9%)	22 (1.6%)
Black	28 (3.5%)	35 (6.0%)	63 (4.5%)
More than one	6 (0.7%)	8 (1.4%)	14 (1.0%)
Unknown	1 (0.1%)	2 (0.3%)	3 (0.2%)
White	763 (94.1%)	529 (90.0%)	1292 (92.4%)
Hawaiian/Other PI	0 (0%)	2 (0.3%)	2 (0.1%)
Ethnicity			
Hispanic/Latino	20 (2.5%)	26 (4.4%)	46 (3.3%)
Not Hispanic/Latino	786 (96.9%)	559 (95.1%)	1345 (96.1%)
Unknown	5 (0.6%)	3 (0.5%)	8 (0.6%)
BMI, kg/m^2			
Mean (SD)	27.4 (4.89)	26.7 (4.57)	27.1 (4.77)
Median [min, max]	26.7 [17.9, 51.6]	26.0 [16.2, 51.3]	26.4 [16.2, 51.6]
BMI category			
Class I obesity	133 (16.4%)	83 (14.1%)	216 (15.4%)
Class II obesity	37 (4.6%)	21 (3.6%)	58 (4.1%)
Class III obesity	21 (2.6%)	9 (1.5%)	30 (2.1%)
Optimum range	259 (31.9%)	217 (36.9%)	476 (34.0%)
Overweight	358 (44.1%)	256 (43.5%)	614 (43.9%)
Underweight	3 (0.4%)	2 (0.3%)	5 (0.4%)
APOE-e4 positivity			
e4−	538 (66.3%)	267 (45.4%)	805 (57.5%)
e4+	231 (28.5%)	250 (42.5%)	481 (34.4%)
Missing	42 (5.2%)	71 (12.1%)	113 (8.1%)

MCI = mild cognitive impairment; SD = standard deviation; PI = Pacific Islander.

Statistical Analyses

Individual differences in within-person change in cognitive function over time and effects of baseline predictors on within-person trajectories of cognitive decline were modeled using Latent Growth Curve Modeling (LGM) (20,21) implemented in MPlus version 7.4 (22). In addition, we tested if the effects of a baseline predictor (BMI) on cognitive decline are global (using a common pathway) or specific (impacting memory, executive function, and language differentially). Model fit was examined using three fit indexes: χ^2 test of model fit, root mean square error of approximation (RMSEA), and comparative fit index (CFI). Good fit was defined as χ^2 not significantly different from the fully saturated model, RMSEA <0.05, and CFI > 0.9. RMSEA values between 0.05 and 0.08 were considered adequate fit. Missing data were accounted for using robust full-information maximum likelihood method (23), a method that consistently outperforms listwise deletion, leading to greater power, less biased parameter estimates, more efficient standard errors, and more accurate type I error rates (24).

The analyses were completed in two steps. First, we compared the fit of linear and nonlinear LGMs to identify the shape of cognitive change trajectories over 4 years of follow-up for each cognitive domain: memory, executive function, and language. LGMs estimate the average patterns of change over time and within-person variation in deviations from mean-level trends. They accomplish this by fitting the following equation: Cognitive Score$[t]_n = y_{\text{In}} + A[t] \times y_{\text{Sn}} + e[t]_n$ for each individual (n) at each time point (t) (20). In this equation, each individual's baseline level of cognitive performance is represented by the intercept (y_{tn}) and within-person change in

cognitive performance over time is represented by the slope (y_{sn}). Both the intercept and slope are free to vary across individuals. The shape of change over time (linear or nonlinear) is estimated by the time-specific basis coefficient $A[t]$, and each individual's deviation from the expected trajectory is estimated by the time-specific residual $e[t]_n$. In a nonlinear model, the shape of the trajectory is free to vary. This is accomplished by setting two basis coefficients to 0 and 1 for scaling purposes and allowing the model to estimate the other time-specific basis coefficients from the observed data. In our analyses, the first basis coefficient was set to 0 and the last basis coefficient to 1; thus, the change score in the nonlinear models represented the amount of cognitive decline over 4 years of follow-up. The change factor was regressed onto the intercept factor in each model. Change factor residual variances therefore represented individual differences in cognitive decline over time beyond variance in changes explained by initial levels of cognitive performance.

In the second step, we investigated if BMI measured at baseline predicts baseline levels of cognitive performance and change in cognitive function over time, over and above baseline diagnosis of CU or MCI. We implemented a factor of curve approach in which shared variance among baseline levels of cognitive functions across domains is represented by a global intercept factor and shared variance among longitudinal changes in cognitive functions across domains is represented by a global change factor. Using this model, we tested if the effects of BMI and diagnosis on cognitive performance at baseline and cognitive change over time can be specified to act through the general intercept and slope factors, respectively (a common pathway model; Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A963), or are best represented as acting directly on the individual domains of cognitive function (an independent pathways model), with BMI and diagnosis affecting memory, executive function, and language differentially. Per analytic plan, we implemented the better-fitting nonlinear models from step 1 into the factor of curve model in step 2. Code is available upon request.

Finally, in an exploratory follow-up analysis, we tested if the effect of BMI on baseline cognitive function and cognitive change over time differed by baseline diagnosis of MCI or CU by a) including the interaction between BMI and diagnosis in the best-fitting model, and b) conducting analyses stratified by diagnosis.

RESULTS

Longitudinal Change in Cognitive Performance by Domain

Based on the univariate growth curve models of each domain individually, on average, participants demonstrated a significant cognitive decline across the 4 years of the study in all three cognitive domains, in terms of their age, sex, and education-adjusted z scores (unstandardized mean change for executive function, memory, and language: $\mu_{exe} = -0.69$, $p < .001$; $\mu_{mem} = -0.47$, $p < .001$; $\mu_{lang} = -0.83$, $p < .001$; Figure 1).

In addition, participants with higher cognitive scores upon entering the study, declined significantly less over the 4 years of follow-up in all three domains (standardized regression coefficient of slope on intercepts: $\beta_{exe} = 0.76$, $p < .001$; $\beta_{lang} = 0.73$, $p < .001$; $\beta_{mem} = 0.22$, $p < .001$; Figure 1).

Model fit statistics were compared for linear and nonlinear LGMs of memory, executive function, and language. The nonlinear models fit better than the linear models with RMSEAs between 0.04 and 0.07 (adequate fit) and CFIs close to 1.00. In addition, all three χ^2 difference tests were significant ($\Delta\ \chi^2_{mem} = 44.42$, $p < .01$; $\Delta\ \chi^2_{exe} = 23.78$, $p < .01$; $\Delta\ \chi^2_{lang} = 59.11$, $p < .01$), indicating a significantly better fit for the nonlinear models as compared with the linear models. Therefore, the nonlinear models were selected for subsequent analyses.

Global Versus Specific Effects of BMI on Cognitive Performance

Next, we fit a factor of curve model, to test if a global cognitive factor can reasonably account for BMI and baseline diagnosis-related changes in memory, executive function, and language and compared it with an independent pathway GLM latent basis model (Supplemental Figure S1, http://links.lww.com/PSYMED/A963). Although both models fit reasonably well, the independent pathway model fit slightly better based on χ^2 model of fit ($\Delta\ \chi^2(13) = 120.65$, $p < .001$), RMSEA ($RMSEA_{common} = 0.05$ [90% confidence interval {CI} = 0.04–0.05] versus $RMSEA_{independent} = 0.04$ [90% CI = 0.03–0.04]), and CFI ($CFI_{common} = 0.98$ versus $CFI_{independent} = 0.99$). Key parameters for both models including global factor loadings can be found in Table 2.

Baseline Diagnosis and BMI as Predictors of Cognitive Performance and Decline Over Time

Finally, we examined if BMI measured at baseline predicted initial levels of cognitive performance and decline in cognitive function over time, over and above baseline diagnosis (CU versus MCI). Table 2 includes partially standardized coefficients for baseline diagnosis and BMI. Participants designated as MCI (diagnosis [Dx] = 1) at baseline exhibited greater cognitive decline over time (partially standardized $\beta_{Dx} = -0.34$, -0.13, and -0.37 [$p < .01$] for executive, memory, and language domain, respectively). Baseline BMI was significantly associated with better memory (partially standardized $\beta_{BMI} = 0.06$, $p < .05$) and worse executive function (partially standardized $\beta_{BMI} = -0.05$, $p < .05$). Baseline BMI was not significantly associated with language performance at baseline (partially standardized $\beta_{BMI} = 0.03$, $p = .159$). Over and above baseline diagnosis of MCI, higher BMI at baseline was associated with a significantly slower rate of cognitive decline over time in all three cognitive domains (partially standardized $\beta_{BMI} = 0.13$, 0.12, and 0.12 for executive function, memory, and language, respectively; $p < .01$). Higher BMI was not associated with the intercept or change in a global cognitive factor (partially standardized $\beta_{BMI} = 0.04$, $p = .059$, for global intercept; partially standardized $\beta_{BMI} = 0.04$, $p = .415$, for global change). The effects of baseline BMI on future cognitive trajectory seemed stronger in the MCI group in the stratified analyses (Supplemental Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A964), but the inclusion of the Dx by BMI interaction in the original model degraded the model fit ($\chi^2(113) = 5258.96$, $p < .001$; RMSEA = 0.18 [90% CI = 0.18–0.19]; CFI = 0.69).

DISCUSSION

In this analysis, we found that, in the ADNI cohort of older adults at risk for AD, higher BMI at baseline (median age = 72 years) was associated with better baseline memory and significantly slower rate of cognitive decline over time in all three cognitive domains. These results are consistent with the tenets of the obesity paradox, which postulates that higher BMI in older age may be neuroprotective. They also support reports from large epidemiological studies with

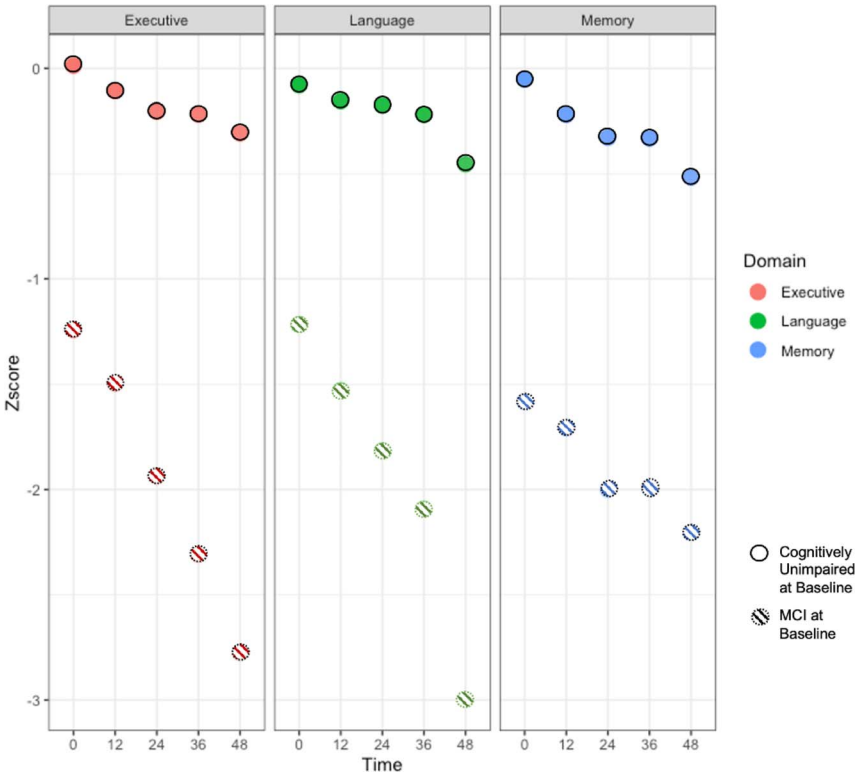

FIGURE 1. Average cognitive performance at each follow-up appointment by domain. Means are generated by MPlus, accounting for potential selective attrition using full-information maximum likelihood method for dealing with missing data. MCI = mild cognitive impairment.

community participants and follow-up periods as long as 28 years (25). As the ADNI cohort was specifically enriched with participants at risk for AD, higher BMI at age 70 years in this context seems to be protective of cognitive function for individuals at high risk for dementia. Inconsistent with the paradox, we found that baseline BMI was associated with poorer baseline executive function and not associated with language. Placing the baseline language results within the context of obesity research is somewhat challenging because language is not often assessed in studies of body weight or composition and is considered relatively stable across the life span (26), possibly through compensatory functional reorganization (27). Poorer executive function in relation to higher baseline BMI, on the other hand, although unexpected in the context of the obesity paradox and the older baseline age of the ADNI participants, fits in with reports that have linked obesity at earlier ages to poorer executive function (11).

The reported discrepancies in the associations between BMI and cognitive function at baseline likely reflect the complexity of the health issues captured by the obesity paradox phenomenon. Late-life cognitive outcomes are also known to be influenced by childhood intelligence, variable influences of obesity on cognitive function by sex (28), and genetic risk for cognitive impairment (29). Weight loss and weight gain may also be a more precise indicator of health outcomes than BMI measured at a single time point anywhere in the life span. For example, Memel et al. (30) reported that, although lower baseline BMI was associated with better cognitive performance even in older age (~75 years), less decline in BMI over time was related to smaller losses of cognitive function. At the same time, a number of studies have reported that the best overall health outcomes (31) and the lowest incidences of dementia (32) are detectable in samples with most the stable weight trajectories and in individuals consistently maintaining recommended weight.

The second issue we set out to investigate in this study was the question of whether obesity has a differential impact on different cognitive domains at baseline and over time, or if cognitive impairment and decline associated with obesity can be accounted for by a single global factor. As discussed earlier, this question is important because it may have implications for understanding the biological mechanisms of obesity-related brain vulnerability and tailoring preventive measures to individuals. We fit a factor of curve model, to test if a global cognitive factor can account for changes in memory, executive function, and language related to late-life obesity and compared it with an independent pathways model. Although the two models were very close in overall fit, and a considerable amount of variance in cognitive function seemed to be accounted for by global factors, BMI showed an effect only on the individual domains. The cognitive results are consistent with a recent meta-analysis of cognitive changes in adulthood, which pooled data from 22 unique data sets including information on more than 30,000 individuals (15). Controlling for dementia, Tucker-Drob and colleagues (15) found convincing evidence for a general factor of cognitive aging with greater than 60% of the variance in longitudinal cognitive change being shared. However, they did not support the hypothesis that obesity-related systemic and central inflammation may converge

TABLE 2. Key Parameters for Common and Independent Pathway Latent Basis Models

Cognitive Factor	Unstandardized Latent Variable Means (SE), Adjusted for BMI and Dx	Unstandardized Residual Variance	Unstandardized Loadings (SE) on a Global Intercept Factor	Unstandardized Loadings (SE) on a Global Change Factor	Standardized Loadings (SE) on a Global Intercept Factor	Standardized Loadings (SE) on a Global Change Factor	Baseline Dx Partially Standardized Coefficients (SE)	Baseline BMI Partially Standardized Coefficients (SE)
Independent pathway model								
Executive intercept	0.38 (0.19)	1.18					−0.48 (0.02)**	−0.05 (0.03)*
Memory intercept	−0.38 (0.13)	0.48					−0.72 (0.02)**	0.06 (0.02)*
Language intercept	−0.28 (0.15)	0.79					−0.53 (0.02)**	0.03 (0.02)
Executive change	−1.42 (0.30)	1.86					−0.34 (0.03)**	0.13 (0.03)**
Memory change	−0.91 (0.19)	0.50					−0.13 (0.05)**	0.12 (0.04)**
Language change	−1.54 (0.32)	2.45					−0.37 (0.03)**	0.12 (0.03)**
Common pathway model								
Executive intercept	−0.15 (0.10)	1.09	0.25 (0.03)**		0.54 (0.02)**			
Memory intercept	−0.28 (0.10)	0.42	0.29 (0.03)**		0.76 (0.02)**			
Language intercept	−0.21 (0.09)	0.72	0.23 (0.03)**		0.59 (0.02)**			
Executive change	−1.36 (0.25)	0.40		0.67 (0.21)**		0.91 (0.03)**		
Memory change	−0.73 (0.10)	0.24		0.25 (0.08)**		0.71 (0.05)**		
Language change	−1.60 (0.30)	0.27		0.80 (0.26)**		0.95 (0.02)**		
Global intercept							−0.92 (0.02)**	0.04 (0.02)
Global change							1.50 (0.43)**	0.04 (0.05)

SE = standard error; BMI = body mass index; RMSEA = root mean square error of approximation; CI = confidence interval; CFI = comparative fit index.

Independent pathway: $\chi^2(102) = 321.21$, $p < .001$; RMSEA = 0.04 (90% CI = 0.03–0.04); CFI = 0.99. Common pathway: $\chi^2(115) = 441.86$, $p < .001$; RMSEA = 0.05 (90% CI = 0.04–0.05); CFI = 0.98.

* $p < .05$.

** $p < .01$.

into a final common pathway leading to global cognitive impairment in obesity via disruption of hypothalamic circuits (14). Thus, our findings support domain-specific effects of obesity on various cognitive functions, likely through independent physiological mechanisms.

Strengths and Limitations

This analysis has several strengths and limitations worth mentioning. Three primary strengths include a large sample size, comprehensive cognitive battery covering multiple cognitive domains, and 4 years of follow-up. ADNI participants are also very well characterized, including comprehensive baseline diagnoses of cognitive impairment and BMI, which was of particular interest in this analysis. A limitation of the ADNI data set is the underrepresentation of African American and Hispanic older adults (the sample is ~95% non-Hispanic White adults) with substantial education (median education is 16 years); thus, our findings may have limited generalizability within the general population of the United States. Another limitation is the use of BMI as an index of obesity. Although BMI is easy to obtain and ubiquitous in the literature, better measures of body composition, such as waist circumference, waist-to-hip ratio, or visceral adiposity, may get us closer to the physiological mechanisms underlying obesity-related cognitive change, as they have been reported to be better predictors of cognitive impairment and dementia than BMI (33,34). Finally, the follow-up period of 48 months is still relatively short, considering the slow progression of cognitive impairment in AD, where changes are often detected in the brain more than two decades before symptom onset (35).

Conclusions

We found that higher baseline BMI was associated with slower cognitive decline in the ADNI cohort. Higher baseline BMI in this context seems to be protective of cognitive function for individuals at high risk for dementia. In addition, we failed to find evidence for a final shared common pathway of cognitive impairment in obesity. Our results are more consistent with multiple physiological mechanisms impacting individual cognitive domains.

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